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ART UNIT	PAPER NUMBER
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Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☒ is extended to run _____ or continues to run 3 months from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed _____ has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: 1
   Claims objected to: _____
   Claims rejected: 21-26

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because Claims 21-26 remain rejected for reasons of record.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other Application is now in compliance with sequence rules.

Bruce Campe

BRUCE R. CAMPE
PRIMARY EXAMIN
GROUP 1800

DETAILED ACTION

Response to Amendment

1. The preliminary amendment filed April 17, 1996 has been entered. Claims 67-107 have been added. Claims 1-107 are pending.

Election/Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-66, drawn to *in vivo* and *in vitro* processes are for example, classified in Class 424, subclass 93.1 as directed to the virus *per se* and Class 514, subclasses 12 and 44 as directed to proteins and polynucleotides *per se*.

II. Claims 67-107, drawn to virus genomic DNA containing heterologous DNA to the virus, i.e., the virus *per se* and cells containing the virus are for example, classified in Class 435, subclass 235.1 and 240.2.

The inventions are distinct, each from the other for the following reasons:

3. The claims of Groups I and II are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product

(MPEP 806.05(h)). In the instant case, the products of Group II have alternative processes of use. See at least claims 54+ which are directed to treating a gene deficiency disorder and the alternative process of use which is treating hepatocellular carcinoma in claims 63+. The claims of Group II are also used in processes for manufacturing the proteins (i.e., an *in vitro* process of culturing the cells to produce the protein) as indicated at page 22 of the present application written description.

4. With regard to the processes of Group I and the compositions of Group II, the election of Groups I or II also require an election of one of the alternatives in each of the following items as appropriate and identification of the claims readable thereon:

(A) *In vivo* (for example, claims 34, 39, 40, 43-45, and 54-62) and *in vitro* (for example, claims 35) because the *in vitro* process can be practiced in the absence of the intact multicellular animal.

(B) Election of *in vivo* in item (A) above requires an election between treating a gene deficiency disorder (for example, claims 54-62) or treating hepatocellular carcinoma (for example claims 63-66) since treating the gene deficiency does not use the same DNA as the treatment for carcinoma nor does treatment for gene deficiency treat a carcinoma *per se*.

(C) Election of *in vivo* or *in vitro* in item (A) and of either alternative in item (B) above also requires an election between protein as the gene product (for example, claims 46-51 which are classified in Class 514, subclass 12) or

antisense (for example, claims 52 and 53) as the gene product since the antisense oligonucleotides that are expressed are not oligonucleotides encoding the protein.

(D) Election of protein or antisense in item (C) above requires an election as to the type of protein or antisense oligonucleotide that is to be delivered which are enzymes, or growth factor related proteins, disease proteins, or clotting factors. Enzymes (see for example claim 49) are not albumin (a blood protein)nor coagulation factors nor is it a growth factor type related protein such as insulin (which would have been classified in Class 536, subclass 23.51) or proteins such as H protein, T protein, or Menkes disease protein, or the product of Wilson's disease protein or pWD or CFTR or an oncogenic related proteins (such as p53 and tumor suppressors), or receptors (claim 99) and toxins (clams 100). Each of the above is directed to a different disease/disorder (see specification pages 18-19). See at least claims 82 and 99).

5. Because these inventions are distinct for the reasons given above and since they have acquired a separate status in the art as shown by their different classification, subject matter, and are separately and independently searched, restriction for examination purposes as indicated is proper.

6. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. 1.143).

7. During a telephone interview with Eldora Ellison by Examiner Christopher Low on or about September 26, 1996, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-66 as directed to processes. Regarding the election of alternatives set forth above, Applicant elected with traverse the "in vitro" processes of element (A) as well as the "protein" gene product of element (C) and the "enzyme" product of element (D). Affirmation of this election must be made by Applicant in responding to this Office action. Claims 34, 39, 40, 42-45, 50-65 and 67-107 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions. Specifically, claims 34, 39, 40, 43-45 and 54-65 are drawn to in vivo processes; claims 52 and 53 are drawn to antisense gene products; and claims 42, 50 and 51 are drawn to non-enzymatic gene products (where claim 42 is interpreted as encoding the asialoglycoprotein receptor). Moreover, claims 49 and 66 will be examined in part and to the extent that they encompass enzymatic gene products.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Drawings

9. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required upon indication of allowable subject matter. See PTO-948 for Draftperson's review.

Double Patenting

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 5-8 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4 of copending Application No. 08/311,157. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 U.S.C. § 112

11. Claims 1-4, 11-33, 35-38, 41, 46-49 and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of expressing an exogenous gene in mammalian cells by use of baculovirus, does not reasonably provide

enablement for methods of expression using other viruses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the teachings of the prior art, the unpredictability in the art, and the amount of direction or guidance presented.

While the specification discloses the recombinant expression of β-galactosidase in mammalian HepG2 cells by use of a recombinant baculovirus, there is no disclosure of other non-mammalian viruses successfully expressing proteins in mammalian cells. Despite assertions in the specification that the other non-mammalian viruses listed in Table 1 can be used in a similar manner, Moyer et al. specifically teach that at least *Amsacta moorei* Entomopoxvirus (AmEPV) "is unable to replicate in vertebrate cell lines" (column 1, lines 52-53). AmEPV is listed as a "Preferred Species" on page 11 of the specification. While recombinant techniques are available to attempt infection of additional mammalian cells with numerous versions of the viruses listed in Table 1, it is not routine in the art to screen large numbers of viruses and cell lines where the expectation of obtaining productive infection and protein expression is unpredictable based on the instant disclosure and taught in the art as being unlikely to be successful. Therefore, the skilled artisan would require guidance, such as necessary viral modifications or the characteristics of mammalian cells which allow productive infections, in

order to make and use expression methods in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

12. Claims 1-25, 31-33, 35-38, 41, 46-49 and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of expressing an exogenous gene in specific mammalian cells by use of a baculovirus, does not reasonably provide enablement for methods of expression in other mammalian cell types, such as mouse cells or human lung carcinoma cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the teachings of the prior art, the unpredictability in the art, and the amount of direction or guidance presented.

While the specification discloses the recombinant expression of β-galactosidase in HepG2, 293 and PC12 cells by use of a recombinant baculovirus, it further discloses that attempts at expression in other mammalian cells resulted in no appreciable enzymatic activity over control levels (see Table 2). Despite assertions that histochemical staining revealed β-galactosidase expression at "low, but reproducible, frequencies" (pg 36, line 21 through pg 37, line 7), there is no disclosure of the detected levels as being the result of *de novo* synthesis or as

being distinct from contaminations from the inoculum used. The virus inoculum data described on pg 42 in this regard is inconclusive since it is limited to HepG2 cells and describes detectable levels of "less than 10% of the expressed after infection" (pg 42, lines 14-15). But a review of Table 2 indicates that even 5% of the level expressed in HepG2 cells (5% of 2.628) is about 18 times higher than that seen in the Jurkat cell line (0.007) which did not express detectable β-galactosidase activity. Given the disclosure presented in the specification, the Examiner is confused as to how the skilled artisan would know that the levels detected by histochemical staining is the result of de novo synthesis or carryover from the viral inoculum. Moreover, these results are consistent with the teachings of Carbonell et al.(AD), where baculovirus mediated infection of human lung carcinoma cells (A549) and mouse fibroblast cells (L929) resulted in no *de novo* expression of an RSV-CAT construct. Similarly, Boyce et al. teach that infection of a variety of cell lines resulted in recombinant expression of β-galactosidase in HepG2 cells only (see pg 2349, Table 1). While recombinant techniques are available to utilize higher concentrations of infectious viruses or modified viruses to infect mammalian cell lines, it is not routine in the art to screen large numbers of modified viruses or cell lines where the expectation of obtaining productive infection and expression is unpredictable based on the instant disclosure. Therefore, the skilled artisan would require guidance, such as necessary viral modifications or the characteristics of mammalian cells which allow productive infections, in order to make and use expression methods in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

13. Any inquiry concerning this communication or earlier communications should be directed to Kawai Lau whose telephone number is 703-308-4209. The examiner can normally be reached Monday-Friday from 7 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax, can be reached at 703-308-4216.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is 703-308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission to the attention of the examiner in Art Unit 1814. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (October 19, 1988) and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The FAX telephone number is 703-305-7401. Note: If applicants do submit a paper by facsimile, the original signed copy should be retained by applicants or applicants' representative. No duplicate copies should be submitted so as to avoid the processing of duplicate papers in the Office.

Kawai Lau, Ph.D.
November 5, 1996

ROBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 180